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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,390	12/17/2001	Manuel Vega	37851-912	5547

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EXAMINER
RIGGINS, PATRICK S

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,390	VEGA ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,62,70,78,94 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,62,70,78,94 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2002 and 14 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Applicant's responses filed 7/6/04, 12/23/04, and 4/14/05 are acknowledged. A number of claims have been deleted (claims 1-44, 47-61, 63-69, 71-77, 79-93), two claims have been amended (claims 45 and 62), and two new claims have been added (claims 94 and 95). Currently claims 45, 46, 62, 70, 78, 94, and 95 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group XXIV in the reply filed on 7/6/04 is acknowledged. The traversal is on the grounds that Group XVIII contains claims generic to Group XXIV and as such newly amended claim 45 (representing Group XVIII) should be treated as a linking claim relative to the species of Group XXIV (represented a s newly amended claim 62). This found to be persuasive and the claims will be treated as such. Thus, claims 45 and 46 are linking claims and claim 62, representing Group XXIV, is a species claim. Applicant further traverses the restriction between Group XXIV (now claim 62) and Group XXV (now claims 70 and 78). These groups will be rejoined. It is noted however, that the remainder of the restriction requirement mailed 3/24/04 is still in effect. To summarize, the claims of former Group XVIII are now considered to be linking claims to the species claims of newly rejoined former Groups XXIV and XXV.

3. Applicant's election with traverse of SEQ ID NO: 113 in the reply filed on 12/23/04 is acknowledged. The traversal is on the ground(s) that the mutations are all in the same protein and the number of sequences to be searched does not exceed 10. This is not found persuasive because as quoted in the response filed 12/24/04, from MPEP 803.04 "up to ten" sequences can be examined in a single application. One sequence is indeed "up to ten". Further, a full search of

all of the possible sequences would place a large strain on the searching capabilities of the Office. As such only SEQ ID NO: 113 has been searched, and the search will not be expanded unless the linking claims are found to be allowable. Thus, claims 45, 46, 62, 70, 78, 94, and 95 are currently under examination, but only with respect to the mutation identified in claim 62 as "T to N at position 350", represented by SEQ ID NO: 113.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

4. The correction to the specification at the Brief Description of the Drawings, Figure 3 has brought Figures 3A and 3B into compliance with the sequence rules. Additionally, the corrected Figures 3A and 3B are acknowledged. It should be noted, however, that the changes to sequence 3 of the figure, alter the consensus (sequence C).

Specification

5. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The Abstract of the instant application in now way reflects the invention that is claimed. The present Abstract appears to be drawn to the directed evolution method that was used to create the adenoviruses of the claimed invention. A new Abstract properly reflecting the invention as claimed is required.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The disclosure is objected to because of the following informalities: page 17, line 30 contains what upon first inspection appears to be a sequence. It appears however, that the amino acids listed are not intended as a sequence, but rather as exemplary. IF this is indeed the case, the individual amino acids should be signified as such and separated, perhaps with commas. If however, this is intended as a sequence, then a proper sequence identifier in compliance with 37 C.F.R. 1.821-1.825 would be required. It is also noted that the Genbank accession numbers referring to the different serotypes of AAV, such as in the paragraph starting at line 3 of page 9 are not in a searchable format. If the accession numbers as listed are searched, not results are returned. Therefore, the appropriately searchable accession numbers are required. Thus changing "NC001729" to --NC_001729--, for example, would be remedial.

Appropriate correction is required.

8. The specification is further objected to because the application is not in compliance with the sequence rules, 37 C.F.R. 1.821-1.825. See the attached Notice to Comply.

Claim Objections

9. Claims 45 and 62 objected to because of the following informalities: Claim 45 recites AAV without first defining what he acronym stands for. The first appearance in the claims of an acronym should be accompanied by the terms for which the acronym stands. Claim 62 contains subject matter that is not part of the elected invention. Further, as claim 62 refers to sequence alterations, the mutant proteins should make reference to the appropriate SEQ ID NO. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 62, 70, 78, 94, and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 62 recites that the mutations comprise replacement of "the native amino acid residue(s)". This lacks proper antecedent basis because it is the nucleic acid molecule that comprises the mutations. Recitation of --...comprising mutations at nucleotide residues, wherein the mutations result in a nucleic acid molecule that encodes a protein comprising replacements of a native amino acid residue...-- or some other similar recitation would be remedial.

Claim Rejections - 35 USC § 112-1

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 45, 46, 62, 70, 78, 94, and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To reiterate, the claims are being examined with respect to the elected species of a T to N mutation at position 350, represented by SEQ ID NO: 113. Thus, the claims are drawn to a nucleic acid molecule which encodes a mutant Rep protein, where the mutation is a T to N mutation at position 350, where the reference point is residue 1 of Rep 78 in AAV-2. The claims are thus drawn to a nucleic acid encoding any mutant Rep protein comprising the equivalent mutation including Rep 78, Rep 68, Rep 52,and Rep 40 from any of the AAV serotypes, including AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5, or AAV-6. The claim are additionally drawn to cells comprising the nucleic acid, recombinant AAV vectors comprising the nucleic acid, and cells comprising the recombinant AAV vector.

15. The specification discloses a method whereby the Rep proteins of AAV-2 undergo a process of directed evolution in a screen to identify mutants that result in alterations in the viral titer. "To identify candidate amino acid (aa) positions on the rep protein involved in rep protein activity an Ala-scan as performed on the rep sequence [from AAV-2]. For this, each amino acid in the rep protein was replaced with Alanine" (page 45, lines 3-6). As was the case with all of the alanine mutations, the mutation of T to A at position 350 resulted in a decrease in viral

production. There is then a table that shows that position 350 in AAV-2 corresponds to position 350 in AAV-1, AAV-3, AV-3b, AAV-4, and AAV-6 and position 346 in AAV-5. "The rep proteins encoded by these sets of nucleic acid molecules were those in which each amino acid position identified as a "hit" in the ala-scan step [including 350], were each sequentially replaced by all remaining 18 amino acids using site directed mutagenesis" (page 52, lines4-8). These mutants were then screened for an increase in AAV production. Among the "leads" identified was the replacement of T by N at position 350. Thus again, sufficient description exists for a T to N mutation in AAV-2, as this is what was exemplified.

16. The question then arises, is possession of this species sufficient to convince the skilled artisan that the inventors wee in possession of the fully claimed genus? In short, no, this would not signify to the skilled artisan possession of the entire genus claimed. Indeed, the specification itself teaches that the mutations identified would not necessarily correlate to mutations in all forms of the rep protein or to the rep proteins of all serotypes of AAV.

17. Referring to Figure 3A, position 350 of AAV-2 is indeed a T residue. In five of the other six serotypes, this position is occupied by an A. Thus, how could the skilled artisan assume that an A to N mutation in any of these serotypes would have the same activity as the exemplified T to N mutation? There is no assurance that these mutations would have the same type of activity. The mutations identified in the instant application to AAV-2 rep are completely random and bear no reasoning for mutating the particular residues. Thus no structure function relationship exists between the identified mutations and the protein. In essence there is no apparent understanding why, for example the T to N mutation that is exemplified has the effect that it does.

18. If indeed this residue is so critical as the viral titer, why then is it not conserved among the different serotypes? Additionally the method that led to the initial identification of position

350 was an alanine scanning method. There is no way this method could have identified position 350 is any of the five other serotypes had been used in this screen. As Figure 3A shows, this position is already an alanine in these other serotypes. If indeed this position were so critical, then wild type AAV-1, AAV-3, AAV-3b, AAV-4, and AAV-6 would necessarily have reduced viral titer relative to AAV-2 or AAV-5, as the initial screen to identify "hits" showed that a T to A mutation at position 350 in AAV-2 resulted in a reduced viral titer. The specification does not teach this and there is no fair suggestion of this difference in the prior art. The skilled artisan would have no reason to believe that the mutation to N at position 350 in AAV-2 would correlate to a mutation to N at position 350 or 346 in any other AAV serotype. Thus, the skilled artisan would find no evidence, based on the specification, as filed, that the inventors were in possession of the full genus of a mutation at position 350 to N in any AAV-serotype.

19. This then leads to the question; does this mutation in the full-length rep protein, Rep 78 of AAV-2 suggest to the skilled artisan that the inventors were in possession of all of the species of rep, including Rep 68, Rep 52, and Rep 40? Again, the short answer is no. It is understood that the different rep proteins of AAV-2 would possess the same T residue at this position, as the differences between the rep proteins are due to differential promoter use and differential splicing, yet all four proteins use the same reading frame. It is further understood that a T to N mutation in Rep 78 would necessarily lead to a T to N mutation is the other three rep proteins. The question then becomes, would each of the individual rep proteins be expected to individually lead to an increase in viral titer? "Rep 52 and 40, the two minor forms of the Rep proteins, do not bind to ITRs and are dispensable for viral DNA replication and site-specific integration" (page 3, line7-9). As Rep 52 and Rep 40 apparently play no role in ITR binding, viral replication, or viral integration, the skilled artisan would have no reason to conclude, absent evidence to the contrary,

that a mutant form of Rep 52 or Rep 40 would be capable of leading to an increased viral titer. Again, there is no teaching in the specification and no finding in the prior art that would suggest that Rep 52 or Rep 40 would have the activity that leads to the increased viral titer seen in the T to N mutation at position 350 of Rep 78. Thus, the skilled artisan would not have reason to believe the inventors were in possession of the invention as broadly claimed.

20. Claims 45, 46, 62, 70, 78, 94, and 95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a mutant form of Rep 78 or Rep 68 of AAV-2 (SEQ ID NO: 113, a cell comprising this nucleic acid, recombinant AAV-2 comprising this nucleic acid, and a cell comprising this recombinant AAV-2, does not reasonably provide enablement for a nucleic acid encoding an equivalent mutation in other AAV serotypes, Rep 52 or Rep 40 comprising this mutation, cells containing this nucleic, recombinant AAV comprising this nucleic acid, or cells comprising this recombinant AAV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. To practice the full scope of this claimed invention, the skilled artisan would be required to perform an undue level of experimentation.

21. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

22. As delineated above, there is no teaching in the specification and no suggestion in the art that a mutation at position 350 to N would necessarily function in the same regard as the T to N mutation exemplified in Rep 78 of AAV-2. The claims are broadly drawn as they encompass any of the versions of the rep protein derived from any of the AAV serotypes. The variation in the residue at position 350, and the apparently unknown function of Rep 52 and Rep 40 means that there is high degree of unpredictability in this regard. The specification exemplifies a T to N o at position 350 in Rep 78 of AAV-2. As argues above, there is no evidence that this would correlate to similar mutations in other serotypes. The specification makes no mention of the sequence differences at position 350 between the different serotypes, except for the alignment in Figure 3. Thus to practice the full scope of the claimed invention, the skilled artisan would be required to partake in an undue level of experimentation. As such, the specification does not enable to skilled artisan to practice the full scope of the instant claims.

Claim Rejections - 35 USC § 101

23. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

24. Claims 45, 46, 62, 94, and 95 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These mutant nucleic acids could certainly be present in the natural reservoir of AAV since the mutations would provide the selective advantage of increase viral production relative to "wild type". Thus these claims are directed to a product of nature. It would be remedial to recite –An isolated nucleic acid—in claim 45, and –the isolated nucleic acid—in claims 46, 62, 94, and 95.

Conclusion

25. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER

Notice to Comply	Application No. 10/022,390	Applicant(s) VEGA ET AL.	
	Examiner Patrick S. Riggins	Art Unit 1636	Page 1 of 1

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequences referred to in claim 62 should be referred to by SEQ ID NO

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
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